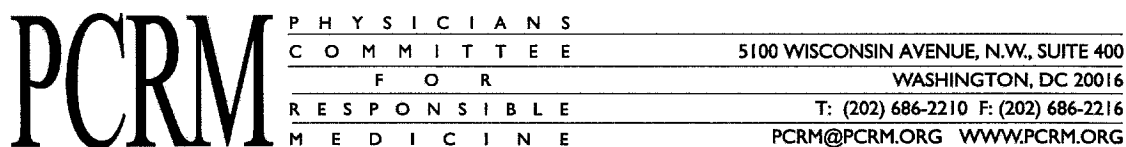


201-15384



June 22, 2004

Michael O. Leavitt, Administrator
U.S. Environmental Protection Agency
Ariel Rios Building, 1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on the HPV Test Plan for Carbonothioic dihydrazide

Dear Administrator Leavitt:

The following comments on Bayer's test plan for the chemical Carbonothioic dihydrazide are submitted on behalf of the Physicians Committee for Responsible Medicine (PCRM), People for the Ethical Treatment of Animals (PETA), the Humane Society of the United States (HSUS), the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

Bayer CropScience LP submitted its test plan on December 29, 2003 for the chemical Carbonothioic dihydrazide (CAS No. 2231-57-4). This compound, also referred to as thiocarbohydrazide, is used as an intermediate in the production of an agricultural herbicide. Bayer has classified this chemical as a closed system intermediate, eliminating the requirement of a repeated dose and reproduction study under the HPV program. The sponsor has asked that a description of closed system intermediate status for this substance remain confidential and we are hopeful that Bayer has provided the EPA with all the relevant information to support this claim.

At this time, we strenuously object to Bayer's proposal to conduct a developmental toxicity test (OECD 414) and an *in vivo* micronucleus study (OECD 474) that will result in the death of at least 1,340 animals. At the very least, if Bayer insists on conducting additional tests for developmental toxicity, we strongly urge the use of OECD 421, the combined reproduction/developmental screen, which will reduce animal deaths by half. The combined protocol is adequate for a screening level program such as HPV and is recommended by the EPA in the Federal Register Notice (FR/Vol. 65, No. 248, Tuesday December 28, 2000). If Bayer wishes to investigate the developmental hazards of this chemical, we ask that the combined study be conducted to spare the lives of 600 animals.

Perhaps even more important, we are surprised to find that Bayer does not mention, or even consider, the potential toxicological relevance of the thiourea component of this chemical's structure. Substantial data exist on the thyroid effects, developmental effects, and potential carcinogenicity of thiourea. Thiourea has been extensively studied and

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additional animal testing with thiocarbohydrazide, which contains thiourea, could be avoided by drawing on the thiourea database. We ask that Bayer review all the available data for thiourea as this information can be used to bridge data gaps for developmental toxicity and chromosomal aberration for thiocarbohydrazide. This approach not only saves the lives of many animals but also demonstrates a thoughtful analysis of the likely toxicity of this chemical based on previous experience with the ethylbisdithiocarbamate class of fungicides, which have another thiourea (ethylene thiourea or ETU) as a common metabolite. There is an extensive database on all EBDCs, as well as ETU.

In addition, we would like to know if Bayer has reviewed a study assessing the acute lethality of 36 semicarbazides and thiosemicarbazides, including thiocarbohydrazide, using the Frog Embryo Teratogenesis Assay: *Xenopus* (FETAX) (Mekenyan *et al.*, 1996). Data from this study, along with hazard data of thiourea-containing compounds, could be used to fulfill the developmental toxicity endpoint for thiocarbohydrazide, thereby eliminating animal testing for this SIDS endpoint.

Finally, it is alarming that Bayer proposes to conduct an *in vivo* genotox test for thiocarbohydrazide when the *in vitro* test for chromosomal aberration (OECD 473) is available. Per EPA guidance (Federal Register, 2000), genetic toxicity tests are to be conducted *in vitro* unless physical properties preclude the use of *in vitro* tests and such justification is documented. If conducted, the *in vivo* test will result in the death of 40 animals.

We request that Bayer reconsider their proposal to kill 1,340 animals in toxicity studies that may be completely redundant for a thiourea-containing compound. Thank you for your attention to these comments. I may be reached at 202-686-2210, ext. 327, or via e-mail at meven@pcrm.org.

Sincerely,

Megha Even, M.S.
Research Analyst

Chad B. Sandusky, Ph.D.
Director of Research

References

Federal Register Vol. 65, No. 248, Tuesday December 28, 2000.

Mekenyen OG, Schultz TW, Veith GD, Kamenska V. 'Dynamic' QSAR for semicarbazide-induced mortality in frog embryos. *Journal of Applied Toxicology* 16(4): 355-363. 1996.